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REVIEW ARTICLE

Intraperitoneal Chemotherapy of Ovarian Cancer: A Review, With a Focus on Practical Aspects of Treatment

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INTRODUCTION

On the basis of the results of three multicenter, randomized, phase III clinical trials, intraperitoneal (IP) chemotherapy has now been shown to be superior to standard intravenous chemotherapy in the primary chemotherapeutic management of small-volume, residual, advanced epithelial ovarian cancer.[1-3] The barriers to implementation of this treatment into clinical practice appear to be toxicity concerns, and a lack of technical expertise with the peritoneal infusion device. The goals of this article are to review the significant scientific evidence behind the rationale for implementing this therapy into routine clinical practice, highlighting the prevention and management of potential toxicities. The surgical and clinical management of the infusion catheters and their complications will be illustrated in detail.

HISTORICAL REVIEW

In 1978, Dedrick et al[4] published a manuscript in *Cancer Treatment Reports* that presented a theoretical modeling study supporting the examination of IP antineoplastic drug delivery as a management strategy for ovarian cancer. In brief, the article suggested that tumors present within the peritoneal cavity could be exposed to cytotoxic drug concentrations one to several logs greater with regional treatment than could be safely attained with systemic drug administration.

This provocative hypothesis stimulated interest within the ovarian cancer research community to begin preclinical evaluation of the strategy, and to initiate phase I studies exploring both the safety and pharmacokinetic advantage of this approach.[5] The early clinical studies confirmed the fact that the peritoneal cavity could be exposed to substantially greater concentrations of cytotoxic agents with known activity in ovarian cancer (eg, 10- to 20-fold for cisplatin and carboplatin; > 1,000-fold for paclitaxel) than possible with systemic delivery.[6-13]

Subsequently conducted phase II trials, the majority of which were cisplatin based, revealed that a proportion of patients with small-volume residual ovarian cancer could achieve a surgically documented complete response to second-line IP chemotherapy when this clinical state had not been achieved in the same individual after primary platinum-based systemic chemotherapy.[5,14] Furthermore, a subset of these patients treated with second-line cisplatin-based IP therapy were reported to experience prolonged survival.[15-18]

However, although of interest, neither the surgically documented response rates nor the observed survival proved the superiority of regional treatment (compared with systemic drug delivery) in patients with ovarian cancer; it could be argued appropriately that any suggested benefits of this approach actually only reflected the natural history of the malignancy in a subset of individuals whose cancers possessed favorable clinical features (eg, small-volume disease with persistent sensitivity to platinum).

PHASE III TRIALS OF CISPLATIN-BASED IP CHEMOTHERAPY AS PRIMARY TREATMENT OF SMALL-VOLUME, RESIDUAL, ADVANCED OVARIAN CANCER

The experience with cisplatin-based second-line IP therapy of ovarian cancer resulted in the initiation of a phase III randomized trial conducted by the Southwest Oncology Group and the Gynecologic Oncology Group (GOG).[1] In this study, patients with small-volume disease (largest residual tumor nodule < 2 cm in maximum diameter) after surgical cytoreduction were randomly assigned to receive either intravenous or IP cisplatin (100 mg/m^2 in both study arms). All patients treated during this study also received intravenous cyclophosphamide.

Patients randomly assigned to the IP cisplatin regimen experienced a lower incidence of neutropenia and tinnitus (presumably from reduced systemic exposure to platinum), but a higher incidence of abdominal discomfort (mostly mild to moderate in severity). The experimental treatment regimen was

associated with a statistically significant improvement in overall survival (median, 49 *v* 41 months; $P = .02$).[1]

Despite the highly favorable results observed in this trial, many theorized that the substitution of intravenous paclitaxel (which subsequently became a standard component of ovarian cancer management) for cyclophosphamide could produce the same degree of improved outcome that was associated with the more complex requirements of regional drug delivery.[19] However, an alternative hypothesis was that IP cisplatin would produce additional clinical benefit, beyond that achieved with an intravenous regimen of cisplatin and paclitaxel.

This important question led the GOG and Southwest Oncology Group (with the assistance of the Eastern Cooperative Oncology Group) to initiate a second phase III randomized trial comparing intravenous versus IP cisplatin-based primary chemotherapy of small-volume residual ovarian cancer after surgical cytoreduction.[2] All patients in this trial received intravenous paclitaxel, in addition to either intravenous or IP cisplatin. It is important to note that in this study, small-volume residual cancer was defined as all remaining tumor masses less than 1 cm in maximum diameter.

The control arm of this trial used the new standard regimen of intravenous cisplatin 75 mg/m^2 plus paclitaxel 135 mg/m^2 administered during 24 hours.[19] The experimental arm included IP cisplatin 100 mg/m^2 plus intravenous paclitaxel 135 mg/m^2 administered during 24 hours.

In an effort to chemically debulk macroscopic residual tumor before the initiation of IP chemotherapy, patients treated on the experimental treatment arm received two cycles of intravenous carboplatin at a moderately high dose (area under the curve 9) before the delivery of the regional treatment program.[20] Unfortunately, although conceptually of interest, the carboplatin resulted in unanticipated severe bone marrow suppression, such that 19% of the patients in this study arm received two or fewer courses of the planned IP regimen, principally because of persistent thrombocytopenia.

Despite this fact, as observed in the phase III trial discussed previously, treatment on the IP cisplatin arm was associated with an improvement in both progression-free (median, 28 *v* 22 months; $P = .01$) and overall survival (median, 63 *v* 52 months; $P = .05$).[2] Thus, even though all patients entered into this study received intravenous paclitaxel, the administration of IP cisplatin further improved survival. (It is relevant to note that although some have suggested this favorable outcome may have partially resulted from the two cycles of higher dose intravenous carboplatin, previously reported randomized phase III trials have failed to demonstrate the benefits of platinum dose-intensity, at least at the drug concentrations that are safely attainable with systemic drug delivery.[21-25]) Although the systemic toxicity observed in this study argued against further development of this specific regimen, or its use in clinical practice, the favorable survival data again emphasized the benefits of regional cisplatin drug delivery in ovarian cancer.

Paclitaxel had been tested previously for IP use in a phase I study, in which the dose-limiting toxicity was abdominal pain.[12] A second IP paclitaxel trial demonstrated the improved tolerability of a lower dose weekly regimen.[13] The GOG subsequently conducted a phase III study using this IP paclitaxel strategy (60 mg/m^2/wk for 16 weeks) in women with a positive second-look laparotomy and less than 0.5 cm residual tumor nodules.[26] Of the 28 patients with microscopic disease only at the beginning of IP treatment, 61% achieved a surgical complete response. Only one of the 31 women with macroscopic residual cancer experienced a complete response.

Thus, with the major pharmacokinetic advantage shown for cavity exposure (> 1,000-fold) after IP delivery of paclitaxel,[12,13] and the activity observed in the second-line setting in microscopic disease,[26] a third randomized phase III trial exploring IP cisplatin-based therapy was initiated by the GOG, which included the addition of IP paclitaxel.[3] The experimental regimen consisted of day 1 intravenous paclitaxel 135 mg/m^2 administered during 24 hours, day 2 IP cisplatin 100 mg/m^2, and day 8 IP paclitaxel 60 mg/m^2. The control arm in this study was again the GOG standard of 24-hour intravenous infusion of paclitaxel 135 mg/m^2 and day 2 intravenous cisplatin 75 mg/m^2.[19]

Although the IP program was associated with more toxicity (myelosuppression, emesis, neuropathy, and abdominal discomfort), treatment with this regimen resulted in a highly statistically significant improvement in both progression-free (median, 24 *v* 18.3 months; $P = .027$) and overall survival (median, 65.6 *v* 49.7 months; $P = .017$).[3] Of note, this study included a formal quality-of-life analysis, and although patients receiving IP therapy experienced a greater short-term decline in this clinical parameter, compared with systemic drug delivery, at 12 months follow-up there was no difference in quality of life between the two treatment groups.[3]

ISSUES WITH THE ADMINISTRATION OF IP THERAPY IN ROUTINE CLINICAL PRACTICE

The results of these well-designed and well-conducted randomized phase III trials have shown clearly that the IP administration of a primary cisplatin-based chemotherapy program favorably and reproducibly influences survival in small-volume, residual, advanced ovarian cancer.

How should the results of these three trials be translated into routine clinical practice? Is it necessary for all patients with small-volume residual ovarian cancer to receive IP cisplatin at a dose of 100 mg/m^2? Can a lower dose be used? Can IP carboplatin be substituted for cisplatin? Is it necessary also to use IP paclitaxel? What is the best catheter system to administer regional treatment? Can an indwelling IP catheter be inserted at the time of primary cytoreductive surgery, or is it necessary for this to be placed after the patient recovers from the initial procedure, especially if a bowel resection has been performed?

As in many areas of oncology, it is difficult to provide definitive answers to these (and other) questions, and future clinical investigation will almost certainly permit many management decisions in this area to be determined by evidence-based guidelines. However, despite this fact, existing data do permit a number of recommendations that should allow for the rational use of this important management strategy.

SURGICAL CONSIDERATIONS AND METHODS OF IP DRUG DELIVERY

Women can now have their venous access device, as well as the IP access device, placed at the same time as the original ovarian cancer resection and staging laparotomy. In the past, particularly when a patient was considered for entry onto a clinical trial, individuals would

only be counseled about chemotherapy postoperatively, and peritoneal access devices would be inserted a few weeks after the laparotomy.

The gynecologic oncologist can now include a thorough discussion of IP chemotherapy during the preoperative counseling and informed consent process. However, it is also important to state that it is quite appropriate for the IP delivery device to be placed after a patient has recovered from the cytoreductive procedure, if this was not accomplished during the initial surgery.

Women who have a successful optimal resection of their cancer may be eligible for clinical trials, which are attempting to optimize the choice of drugs, doses, and schedules of IP chemotherapy. Patients not enrolled onto clinical trials can be offered standard-of-care IP chemotherapy, and therefore need to be informed about the ports that are required for administration, should the surgery be optimal and without complications. The intraoperative decision has to be made about whether it is appropriate and in the patient's best interest to proceed with placement of these devices.

Although patients with microscopic residual cancer who have not undergone a bowel resection might be considered the ideal candidates for IP chemotherapy, existing data clearly demonstrate the benefits of treatment in the presence of larger volume, optimally debulked disease. In addition, the requirement for a bowel resection during surgical cytoreduction should not generally prevent a patient from receiving this management strategy.

If it can be avoided, it is advantageous not to enter the vagina by performing a supracervical hysterectomy. However, if removal of all gross disease requires entry into the vagina, accomplishing this goal should be considered a priority. If the vagina is opened, care must be taken to ensure the closure is water tight with delayed absorbable suture, to avoid leakage of peritoneal chemotherapy out the vagina. The abdominal wound can also leak ascites and IP chemotherapy if treatment is initiated early, so the same considerations apply.

There are advocates of adhesion barriers, such as Seprafilm (Genzyme Biosurgery, Cambridge, MA), to improve distribution of chemotherapy in the abdominal cavity, but the potential benefits have not been validated in a randomized trial.

Treatment during the early postoperative period has been studied and is feasible,[27] but most surgeons allow the patient to recover fully from the ileus, documented by normal bowel function, and indicate that the patient should tolerate a regular diet to ensure that there have not been operative complications. A theoretical advantage of early treatment is to try to infuse the chemotherapy drug before dense adhesions have occurred at the operative sites, which prohibit the IP chemotherapy from bathing residual tumor, but this is unproven.

The insertion of a drug delivery device at the time of laparotomy should only add 15 to 30 minutes to the operative time. The device should be a fully implantable port attached to a single lumen venous silicone catheter of large size (9.6 French) so it will not kink and obstruct inflow (Bardport; C.R. Bard Inc, Murray Hill, NJ, or Deltech Inc; Smith's Medical MD Inc, St Paul, MN). Peritoneal catheters with fenestrations and Dacron cuffs should be avoided (portocath peritoneal catheters or Tenckhoff catheter). The Dacron cuffs have been seen to erode into the peritoneal cavity and be associated with bowel obstructions. The fenestrated catheters appear to encourage fibrous sheath formation and bowel adhesions. These types of devices cannot be removed easily in the office under local anesthesia; after the last cycle of IP chemotherapy is completed, the catheter should be removed to avoid future complications.

Ports should be placed on the inferior thorax at the midclavicular line, below the location where a bra may irritate the area. This site allows ease of access with a Huber needle, and the device can be removed easily under local anesthesia, without entering the peritoneal cavity. A transverse incision slightly larger than the port is made overlying the lower rib, and a subcutaneous pocket is created over the fascia covering the ribs. The port is sutured with 2-0 Prolene at four corners to the fascia to prevent rotation resulting in Huber needle access problems. Alternatively, some surgeons elect to use absorbable suture material, relying on fibrous tissue that subsequently forms to hold the device in place.

The catheter should be tunneled subcutaneously, above the fascia, 6 cm lateral to the umbilicus and pulled into the peritoneal cavity through a small hole the size of the catheter (use a catheter tunneling device or a tonsil clamp). The catheter should be cut to allow 10 cm of catheter within the peritoneal cavity, to ensure it remains in the abdominal cavity, and the port should be flushed with 10 mL of heparin 100 U/cm^3.

There may be occasions when the insertion of the access device should be delayed, such as an unclear diagnosis, gross bacterial contamination of the peritoneal cavity, serious comorbidities, or intraoperative complications. In general, it is easier to remove a device that is not needed than it is to place one at a second surgery. Another advantage is that chemotherapy can be initiated in a timely fashion if the access device is in place. However, it is always important for clinicians to use their own judgment about whether the best course of action in an individual patient is to delay catheter placement.

Bowel resections are performed on 30% of patients with optimally resected stage III ovarian cancer[28] because of the strong belief in the gynecologic oncology community of the concept of maximum surgical effort to obtain minimal residual disease in women with ovarian cancer. These procedures can be associated with gross contamination of the operative field, postoperative infections, abscesses, fistulas, and leaks at anastomotic sites. There is no absolute contraindication to placement of the access device at the time of a bowel resection, but because of the potential complications, including catheter infections, some prefer delayed insertion.

The delayed insertion has the associated problem of difficulty identifying free IP space where the bowel may be adherent to the underlying peritoneal surface. It is advisable to avoid the previous midline incision, and make an incision 6 cm lateral to the umbilicus to avoid the transverse colon, which will be adherent to the anterior abdominal wall after an omentectomy. The right side is usually preferred, unless there has been an ileocecal resection. Under direct visualization of the peritoneal structures to avoid injury, the catheter is pulled through the abdominal wall from the subcutaneous tissue into the peritoneal cavity with a tonsil or a tunneling device to keep the perforation as small as possible. The catheter should not be inserted directly through the incision into the peritoneal cavity or it will leak fluid retrograde back into the port pocket. The wound should be closed in separate layers to avoid leakage. The catheters come preattached to the port or attachable; the attachable version gives the surgeon more flexibility in choice of techniques for delayed insertion. The port placement is otherwise the same as the open procedure. The peritoneal chemotherapy should be delayed at least 24 hours. Avoiding injury to the bowel is the key to successful placement.

Specific techniques also are described for interventional radiology[29] or laparoscopic insertions.[30]

PREVENTION OF COMPLICATIONS OF IP CHEMOTHERAPY ADMINISTRATION

IP chemotherapy is discontinued prematurely for three main reasons: problems related to the access device, abdominal pain with infusion, and intolerance to the higher dose cisplatin. Many of these problems are disease related, given that patients may present with a large volume of tumor and poor nutritional status, and have intra-abdominal adhesions from surgery.

Some problems potentially are avoidable, such as difficulty getting the Huber needle into the port, kinking of the catheter, retrograde flow of fluid into the port pocket, leaking of fluid out the vagina, bowel injuries, and port infections. The surgical technique outlined is designed to minimize these complications. When catheters fail, attempts to replace them are often unsuccessful unless the specific cause of failure, such as a rotated port, is easy to remedy.

Abdominal pain that occurs with IP chemotherapy administration is believed to be secondary to stretching and distention of bowel-to-bowel adhesions. The chemotherapy is generally mixed in 1 L of normal saline and warmed to 37°C, and infused through the port via gravity drip as rapidly as possible. A second liter of saline is then administered to help distribute the drug to all sites in the peritoneal cavity. If pain is encountered, the second liter can be reduced in volume or not given. The rate of flow can be reduced as well. The symptom of pain is evidence that the distribution of drug is likely to be less than ideal—it could be caught in a small-volume pocket of adhesions. Interest in developing interventions to combat this problem has not as yet yielded favorable results.

There may be more pain and increased adhesions with IP paclitaxel; the rate of cessation of IP chemotherapy was higher in the trial in which paclitaxel was infused into the abdominal cavity.[3] This hypothesis is being investigated in a recently approved clinical trial to be conducted by the GOG.

Patients must receive effective antiemetics for cisplatin chemotherapy. The systemic exposure to the agent after IP delivery is comparable to intravenous administration.

It is critically important that the clinician pay special attention to the patient's intravascular volume. The first cycle of chemotherapy is likely to be delivered to a malnourished woman, possibly with a low albumin level, peripheral edema, and ascites. This total body fluid excess (third spacing) is associated with a poor intravascular volume.

Prehydration of the intravascular compartment with 1 L of normal saline and a urine output of 100 mL/h should be the minimum routine before infusion of cisplatin into the peritoneal cavity. The addition of 2 L of IP normal saline does not replace the need for adequate hydration before and after cisplatin and the maintenance of excellent urine output. Avoiding dehydration due to emesis after cisplatin will help prevent renal toxicity. The first cycle frequently is the most challenging, and within 2 to 3 weeks of the first administration of IP cisplatin, the nutritional condition of the patient will likely improve markedly and the third spacing will resolve.

It is important to recognize the significant potential for neurotoxicity associated with the combination of cisplatin and paclitaxel.[3,21,31] Of note, short paclitaxel infusions (eg, 3 hours), delivered on the same day as cisplatin 75 mg/m^2, are known to increase the risk of highly clinically relevant neuropathy.[31] Dose reduction when symptoms of neurotoxicity are first observed may permit more cycles of IP cisplatin to be administered.

It is also important to emphasize that there are reported complications related to IP catheters in patients not receiving IP chemotherapy. Unlike the venous systems, the catheter does not serve a useful purpose once the patient either has been treated successfully and is clinically free of disease or experiences disease progression. It is advisable to remove the device when treatment is completed to prevent unnecessary complications. This can be accomplished in 15 minutes with local anesthesia and minor surgery equipment to open the previous incision down to the port, cut and remove the permanent sutures, and pull out the device. The silicone venous catheter pulls out of the track and peritoneal cavity without difficulty, and is not adherent to bowel, like Tenckhoff catheters.

RECOGNITION, DIAGNOSIS, AND MANAGEMENT OF IP CHEMOTHERAPY COMPLICATIONS

Catheter-related complications have been observed in up to one in five patients, including port access problems, inflow obstruction, leakage around the port or into the surrounding subcutaneous tissues, infection, and IP fluid leaking out the vagina, wound, or even through the GI tract. Specific port site complaints are evaluated and managed in a manner similar to that for a venous access device.

The port should not be too small or too deep in the subcutaneous tissues, if it is placed on the lower ribs, and should be easily palpable. The inability to access the port is best evaluated with fluoroscopy to determine if the Huber needle can be directed through the diaphragm of the port into the reservoir. Contrast can be injected and observed with fluoroscopy to ensure catheter integrity and patency, demonstrating flow into the peritoneal cavity. This methodology can also demonstrate adhesions, dye backflow along the catheter into the port pocket, and dye entering the GI tract.

Treatment of the specific problem, or abandoning the route of delivery of the chemotherapy, should be considered patient-specific decisions. Port revisions can be simple to perform or nearly impossible. The rotation of a port making access difficult is an easily correctable problem, whereas backflow along the catheter is not correctable without choosing a new peritoneal infusion site.

Replacing a malfunctioning port has allowed 50% of patients to complete their planned IP chemotherapy, but requires a commitment of the patient and the enthusiasm of the surgeon. Contraindications to replacement include peritonitis, intra-abdominal abscess, GI injury, or fistula.

Abdominal pain is a common complaint of the IP chemotherapy patient, but in most cases is related to the infusion and distention of the abdomen, especially when the symptoms develop immediately after delivery of the treatment volume.

Peritonitis or GI injury should be considered in the case of guarding, rebound, nausea, vomiting, diarrhea, fever, or elevated WBC count. Peritonitis or GI injury can be evaluated by irrigation of the catheter with 5 mL of normal saline and aspiration of the specimen for cell count and culture. An acute abdominal series radiologic examination can find free air and fluoroscopy can determine the location of the catheter infusion. Removal of the port and catheter is advised when

infections are encountered, as well as antibiotic therapy, which treats skin and GI flora. Bowel complications may require antibiotics, total parenteral nutrition, and bowel rest or surgical intervention, depending on the circumstances.

In limited series, paclitaxel has been associated with 2.3% intestinal perforation rate and a 43% mortality secondary to this complication when unrelated to IP chemotherapy.[32,33] Evaluation may require computed tomography scan or immediate surgical intervention. It is believed that subclinical surgical complications or the patient's natural ability to control small leaks or infections is overwhelmed by paclitaxel chemotherapy, and these complications are usually unmasked 2 weeks after the first or second chemotherapy cycle. Recognition, timely diagnosis, and appropriate treatment in these occurrences save lives.

Leakage of fluid out of surgical wounds, including the vagina, can spontaneously heal if venous treatment is given for the first cycle. Leakage of fluid out the rectum may require GI diversion (colostomy, ileostomy) and abandoning of IP chemotherapy.

USE OF CISPLATIN AND IP CISPLATIN DOSING

The majority of oncologists prefer to use carboplatin, rather than cisplatin, because of the ease of administration, the avoidance of renal toxicity and severe nausea and vomiting (both acute and delayed), and the lower risk of neurotoxicity.[34,35] Furthermore, the IP programs discussed have significant toxicity when compared with the previous standard intravenous regimen of carboplatin and 3-hour infusional paclitaxel.[36-38]

However, with the substantial survival benefit documented in these well-designed and conducted randomized phase III trials, it is incumbent on the oncology community to determine how we can translate the results of the above noted trials into routine care for our patients with small-volume, residual, advanced ovarian cancer. Although all three randomized trials used an IP cisplatin dose of 100 mg/m^2 and demonstrated the feasibility of this regimen, considerable platinum-related systemic toxicity (eg, emesis, neurotoxicity) was observed.

As noted previously, several randomized trials have convincingly shown that there is no significant impact of platinum dose-intensity at the concentrations of drug achieved in the systemic compartment after intravenous drug delivery.[21-25] Furthermore, examination of the literature regarding cisplatin dosing demonstrates the rather steep dose-response effect for the production of serious toxicity, especially emesis.[34,35] In fact, in the most recent IP randomized trial, much of the difference in the observed systemic adverse effects between the regimens may have been attributable to the cisplatin dosing, where patients on the intravenous arm received cisplatin at a dose of 75 mg/m^2 versus the 100 mg/m^2 dose used in the IP regimen.[3]

Thus, it may be reasonable to suggest that by simply reducing the dose of IP cisplatin to 75 or 80 mg/m^2, the tolerability of the regimen may be substantially improved, without interfering with the documented benefits associated with regional drug delivery. Major justification for this statement comes from the fact that with IP drug administration, the 10- to 20-fold higher concentration of the cytotoxic agent will still be in direct contact with the tumor within the peritoneal cavity, even though the systemic exposure is reduced modestly.[6-9]

IP CISPLATIN VERSUS IP CARBOPLATIN

Because it is known that intravenous carboplatin and cisplatin have equivalent efficacy against ovarian cancer,[34-38] that IP carboplatin can be safely administered with a similar pharmacokinetic advantage compared with IP cisplatin,[10,11] and that IP carboplatin has been shown to produce objective responses when delivered by the IP route,[39-41] why not simply substitute IP carboplatin for IP cisplatin? In view of the substantial survival advantage demonstrated for IP cisplatin in three randomized trials, it would be premature to assume IP carboplatin is equivalent to IP cisplatin, despite the evidence with systemic administration.

Observed disparities in platinum-tissue concentrations between the agents after regional delivery in preclinical evaluation heightens concern for potential clinically meaningful differences between the drugs in this setting.[42] It is hoped that a future randomized trial will compare directly an IP carboplatin-based chemotherapy regimen versus an IP cisplatin regimen, but based on existing data, cisplatin should be the platinum agent considered to be the standard of care for regional therapy in ovarian cancer.[1-3]

For an individual patient who receives IP cisplatin-based therapy and who experiences unacceptable systemic cisplatin-associated toxicity (eg, emesis), it may be reasonable to use IP carboplatin instead of IP cisplatin to maintain the benefit of the IP approach with potentially less toxicity. In such a situation, based on previously published data, a regimen of IP carboplatin (area under the curve 6) plus intravenous paclitaxel (175 mg/m^2 during 3 hours) might be considered.[41] However, because the benefit of IP carboplatin has not yet been proven in a randomized trial, the use of conventional IV paclitaxel and IV carboplatin for patients who cannot tolerate the IP approach is a reasonable option as well.

A ROLE FOR IP PACLITAXEL

Probably the most difficult question to address at present is the role of IP paclitaxel in a primary ovarian cancer regional treatment program. Although the most recently reported randomized trial,[3] which revealed the greatest survival difference between the study arms, did include IP paclitaxel, the two previous phase III studies that also demonstrated statistically significant survival benefits associated with regional treatment[1,2] did not deliver this drug regionally. Furthermore, it is possible that much of the local toxicity observed in the recent trial resulted from the IP administration of this agent.

Thus, although the most recent data would support the delivery of IP paclitaxel, an alternative approach would be to administer this agent only by the systemic route for the initial treatment course, and if the patient is able to tolerate regional cisplatin treatment (eg, no or minimal local toxicity), then IP paclitaxel could be added with subsequent cycles. Conversely, if the initial course of IP cisplatin produces modest local discomfort, it may be prudent to avoid the IP delivery of paclitaxel, which may increase that discomfort substantially.

In conclusion, much remains to be learned regarding the optimal IP therapeutic program and drug delivery strategy for the treatment of small-volume, residual, advanced ovarian cancer. However, it is also critically important to state that a large body of existing data reveals this is a management approach that can be administered safely and

effectively in routine oncologic practice, outside the setting of a clinical trial or a tertiary medical center. Furthermore, although the delivery of IP therapy may require modifications of existing treatment paradigms and development of new skills, it is essential to remember that the unquestionable beneficiary of this effort will be the patient with ovarian cancer.

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The authors indicated no potential conflicts of interest.

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